PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Anaesthesia-related complications and side-effects in TAVI: a retrospective study in Germany
AUTHORS	Goldfuss, Sophia; Wittmann, Sigrid; Würschinger, Fabian; Bitzinger, Diane; Seyfried, Timo; Holzamer, Andreas; Fischer, Marcus; Camboni, Daniele; Sinner, Barbara; Zausig, York

VERSION 1 - REVIEW

REVIEWER	Mehdi Eskandari King's College Hospital, London, UK
REVIEW RETURNED	04-Sep-2018

GENERAL COMMENTS	In this manuscript Goldfuss et al report anaesthesia related complications and side effect in 853 patients that underwent TF and TA TAVI from 2009-2015 in a single center. There has been a significant trend towards the local anaesthesia/concious sedation in TF TAVI. Several single centre studies and reports from big registries have compared the two methods and it have shown that local anaesthesia/conscious sedation is safe in TF TAVI. and that there is no difference between the two methods with regard to mortality and procedural outcome. The GA has been associated with longer hospital admission and procedural time. TA TAVI that comprises close to half o the patients in this cohorts is rarely performed these days and the data concerning this method is outdated. There is a lot of data presented in the manuscript in relatively disorganised way including the impact of some of the reported side effects on mortality/ length of stay that could have been a seperate section for presenting results. More importantly, it's not clear if other relevant confounding factors such as acute kidney injury has been taken into account or not? The inflammatory response in TAVI also plays an important role in some of the complications especially in TA approach regardless of the GA and merits discussion . In this regard, the type of the valve used and the percentage of the rapid pacing and balloon valvuloplasty should have been reported. There are several grammatical errors and the manuscript needs major edition from an English language point of view. Comments: 1- Abstract needs major revision in presenting results/discussion and conclusion. They authors state "Only 3% suffered from anaesthesia-related complications.These complications were only minor ones without clinical relevance."

	The complication rate has been described 3.8% in TF and 1.4% in TA TAVI in the result section (2.8% TA/TF cases) ncluding a cardiac arrest , airway damage and laryngospasm that is considered as only minor events. “In this study, serious anaesthesia-related complications were not seen” - It’s not clear what the authors mean by serious anaesthesia -related complication but there was a patient with cardiac arrest. 2-In the strength and limitations of the study the authors do not point out any strength! 3- Page 4 , BMI and NYHA are used as only abbreviation and should be full word in their first use in the manuscript. 4- Page 8 - result section: “Serious complications were rarely seen.” The interpretation of the presenting results should be in the discussion. 5- Table 2: the percentage of complications/side effects should be inserted in front of the numbers to be consistent with the rest of the table 6- The second paragraph , in the section Results- Delirium, is disorganised. Impact of complications/side effects on length of stay itself as well as mortality could be a seperate paragraph. 7- TAVI started with GA and the are even some reports that the intra-procedural TEE that goes hand in hand with the GA may have a positive impact on the procedure. Therefore the conclusion in fact does not add much to the literature as GA has been considered a safe option in TAVI with the caveat that it adds to the length of stay and procedure time.

REVIEWER	Gereon Schälte Dept. of Anesthesiology University Hospital RWTH Aachen, Aachen Germany
REVIEW RETURNED	15-Sep-2018

GENERAL COMMENTS	Dear All, I have read your manuscript and results with pleasure. This is one of the few manuscripts focussing on isolated anesthesia related complications in TAVI and not mixing them up with intervention associated outcome variables. Most of the limitations and my concerns after reading the first paragraphs have been addressed in the discussion (e.g. concerns regarding the detection of delirium, pre-interventional cognitive state). There are only a few questions I would like you to comment on: page 10 line 54: how do you explain the significant incidence of delirium between TA- and TF-TAVI group? Please refer and explain in the discussion. page 11 line 52: what is your rationale for premedication? These patients are poly-morbid in general and have a high incidence of PAH...? Please comment. page 13 line 14: Please comment on the effect of weight and TA-TAVI as a risk factor for hypothermia. The is hardly to understand and is suspect to a systematic fault in temperature management and the procedural approach.

	Please discuss your overall findings in comparison with the recent publications on TAVI and general anesthesia

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Mehdi Eskandari

Institution and Country: King's College Hospital, London, UK

Please state any competing interests or state ‘None declared’: None declared

Thank you for your advice, we changed that accordingly.

Please leave your comments for the authors below

In this manuscript Goldfuss et al report anaesthesia related complications and side effect in 853 patients that underwent TF and TA TAVI from 2009-2015 in a single center. There has been a significant trend towards the local anaesthesia/concious sedation in TF TAVI. Several single centre studies and reports from big registries have compared the two methods and it have shown that local anaesthesia/conscious sedation is safe in TF TAVI. and that there is no difference between the two methods with regard to mortality and procedural outcome. The GA has been associated with longer hospital admission and procedural time.

TA TAVI that comprises close to half of the patients in this cohorts is rarely performed these days and the data concerning this method is outdated. There is a lot of data presented in the manuscript in relatively disorganised way including the impact of some of the reported side effects on mortality/ length of stay that could have been a seperate section for presenting results.

We have revised the manuscript, and hope that the presentation is now more pleasant.

More importantly, it’s not clear if other relevant confounding factors such as acute kidney injury has been taken into account or not?

As stated in the method section this is a second manuscript of a large retrospective study at our hospital. In the first, already published, manuscript we looked at intervention-related complications. There you will find AKI, etc. However, in this manuscript we focused on the anaesthesia-related factors. To make it clearer we have now revised the manuscript in the method section.

The inflammatory response in TAVI also plays an important role in some of the complications especially in TA approach regardless of the GA and merits discussion. In this regard, the type of the valve used and the percentage of the rapid pacing and balloon valvuloplasty should have been reported.

Thank you very much for this important annotation. Unfortunately, our study design did not focus on this prominent item in context with anaesthesia-related complications or side-effects. In the first, already published manuscript we have information about the valves used in the study. Therefore, we have revised our manuscript and have linked to the information of the valves used in this study.

There are several grammatical errors and the manuscript needs major edition from an English language point of view.

We have carefully screened the manuscript and revised the manuscript in this regard.

Comments:

1- Abstract needs major revision in presenting results/discussion and conclusion.

They authors state “Only 3% suffered from anaesthesia-related complications. These complications were only minor ones without clinical relevance.”

The complication rate has been described 3.8% in TF and 1.4% in TA TAVI in the result section (2.8% TA/TF cases) including a cardiac arrest , airway damage and laryngospasm that is considered as only minor events.

We revised the method section, result section and the abstract, to make clear, how side-effects and complications were defined.

“In this study, serious anaesthesia-related complications were not seen” - It’s not clear what the authors mean by serious anaesthesia -related complication but there was a patient with cardiac arrest.

Thank you for your comment. We did not find any anaesthesia-related reason for the cardiac arrest, we revised the section to make that clearer.

2-In the strength and limitations of the study the authors do not point out any strength!

The strengths of our manuscript are:

• We can provide reliable data because of the large study size.

• Multivariable analysis was used to minimise confounding bias.

• This manuscript focusses on anaesthesia-related complications and side-effects in TAVI patients.

3- Page 4 , BMI and NYHA are used as only abbreviation and should be full word in their first use in the manuscript.

Thank you. We changed that.

4- Page 8 - result section: “Serious complications were rarely seen.” The interpretation of the presenting results should be in the discussion.

You are right with that point. We deleted that sentence.

5- Table 2: the percentage of complications/side effects should be inserted in front of the numbers to be consistent with the rest of the table.

Thank you for your annotation. Some patients suffered from more than one complication or side effect. So unfortunately we cannot give the percentage of complications/side effects. We stated this out in the legend and linked the percentages in the main text. We hope you are satisfied with this solution.

6- The second paragraph , in the section Results- Delirium, is disorganised. Impact of complications/side effects on length of stay itself as well as mortality could be a seperate paragraph.

Thank you. We revised that paragraph.

7- TAVI started with GA and the are even some reports that the intra-procedural TEE that goes hand in hand with the GA may have a positive impact on the procedure. Therefore the conclusion in fact

does not add much to the literature as GA has been considered a safe option in TAVI with the caveat that it adds to the length of stay and procedure time.

This is a very important comment. Therefore, with a revised the manuscript in this regard in the introduction and conclusion section.

Reviewer: 2

Reviewer Name: Gereon Schälte

Institution and Country: Dept. of Anesthesiology, University Hospital RWTH Aachen, Aachen, Germany

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Dear All,

I have read your manuscript and results with pleasure. This is one of the few manuscripts focussing on isolated anesthesia related complications in TAVI and not mixing them up with intervention associated outcome variables.

Most of the limitations and my concerns after reading the first paragraphs have been addressed in the discussion (e.g. concerns regarding the detection of delirium, pre-interventional cognitive state). There are only a few questions I would like you to comment on:

page 10 line 54: how do you explain the significant incidence of delirium between TA- and

TF-TAVI group? Please refer and explain in the discussion.

Thank you. We added several reasons in the discussion section.

page 11 line 52: what is your rationale for premedication? These patients are poly-morbid in general and have a high incidence of PAH...? Please comment.

You are right, the usefulness of premedication is currently under discussion. The results of our study have changed our regime in Regensburg. Therefore, premedication is no longer in use in TAVI patients.

page 13 line 14: Please comment on the effect of weight and TA-TAVI as a risk factor for hypothermia. The is hardly to understand and is suspect to a systematic fault in temperature management and the procedural approach.

We also had that idea. We reacted to that problem over time by introducing a warming system with a focus on prewarming. We added a section to the manuscript.

Please discuss your overall findings in comparison with the recent publications on TAVI and general anesthesia

We have revised our manuscript and emphasize now the discussion on GA in TAVI.

VERSION 2 – REVIEW

REVIEWER	Mehdi Eskandari KIng's College Hospital - London
REVIEW RETURNED	27-Jan-2019

GENERAL COMMENTS	The authors have addressed the reviewers' comments and the manuscript reads better. A few minor suggestions: Could I ask please to change “TAVI in general anaesthesia” to “TAVI under general anaesthesia” in the abstract and the text. Could author please add the mean age of patients in the result section in the abstract. If the you are above the word limit the first sentence in the result section can be deleted as the number of participants has been reported in method. In the results section in the abstract : “2.8% (n=24) of all cases suffered from anaesthesia-related complications. 819 anaesthesia-related side effects occurred in 586 (68.7%) patients. These side effects did not have any serious consequences either.” The word either at the end of the sentence above does not make sense. I suspect the authors meant neither complications nor side effects resulted in mortality? Please include the number of TA and TF patients in the results in the abstract Statistics - last sentence - please change the “two groups “ to the name of the groups as they have not been mentioned earlier in the paragraph. Results table 1 - not sure what restriction refer to - please specify Reflux - If the authors mean GORD please write the full word

REVIEWER	Gereon Schälte University Hospital RWTH Aachen Dept. of Anaesthesiology Pauwelsstr. 30 52074 Aachen Germany
REVIEW RETURNED	11-Jan-2019

GENERAL COMMENTS	Your quality of manuscript has very much improved and as previously stated, this is one of the few publications focussing typical anaesthesia related side effects. Unfortunately, due to your institutional protocols you could not present data comparing GA vs LA side effects and present these data. My concerns have appropriately been answered and current evidence was implemented in the discussion. From my point of view your manuscript would benefit from professional editing and this is my last concern. For I'm not a native speaker the editors should decide if the quality of English publication ready. If so, my suggestion would be "accept".

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Gereon Schälte

Institution and Country: University Hospital RWTH Aachen - Germany

Please state any competing interests or state ‘None declared’: None declared

Thank you for this important advice. We already added this in the first revision. The section is placed after “Conclusion”.

Please leave your comments for the authors below

Your quality of manuscript has very much improved and as previously stated, this is one of the few publications focussing typical anaesthesia related side effects. Unfortunately, due to your institutional protocols you could not present data comparing GA vs LA side effects and present these data.

My concerns have appropriately been answered and current evidence was implemented in the discussion.

From my point of view your manuscript would benefit from professional editing and this is my last concern. For I'm not a native speaker the editors should decide if the quality of English publication ready. If so, my suggestion would be "accept".

Thank you very much. We have already had proofreading by a native speaker. Additionally, we have revised again the manuscript and are now very satisfied with the result. If no one has any complaints, we would like to leave the manuscript that way.

Reviewer: 1

Reviewer Name: Mehdi Eskandari

Institution and Country: King's College Hospital - London

Please state any competing interests or state ‘None declared’: None

Thank you for this important advice. We already added this in the first revision. The section is placed after “Conclusion”.

Please leave your comments for the authors below

The authors have addressed the reviewers' comments and the manuscript reads better. A few minor suggestions:

Could I ask please to change “TAVI in general anaesthesia” to “TAVI under general anaesthesia” in the abstract and the text.

Thank you for this important advice. We changed this accordingly.

Could author please add the mean age of patients in the result section in the abstract. If the you are above the word limit the first sentence in the result section can be deleted as the number of participants has been reported in method.

In the results section in the abstract : “2.8% (n=24) of all cases suffered from anaesthesia-related complications. 819 anaesthesia-related side effects occurred in 586 (68.7%) patients. These side effects did not have any serious consequences either.”

The word either at the end of the sentence above does not make sense. I suspect the authors meant neither complications nor side effects resulted in mortality?

Please include the number of TA and TF patients in the results in the abstract

Thank you for your essential annotations concerning the abstract. We revised this section and hope that the abstract is now more pleasant.

Statistics - last sentence - please change the “two groups “ to the name of the groups as they have not been mentioned earlier in the paragraph.

Thank you for this important comment. We revised this section as well.

Results table 1 - not sure what restriction refer to - please specify

Reflux - If the authors mean GORD please write the full word.

Thank you for your recommendations regarding Table 1. We changed this table accordingly.